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(54) Title: PROSTAGLANDIN E2 TREATMENT OF IMPOTENCE

(57) Abstract

Disclosed are compositions and methods for the treatment of male impotence, wherein erectile dysfunction is alleviated by administering a pharmaceutically acceptable formulation containing prostaglandin PGE_2. An antidote for the effects of administration of the PGE_2, or for treating priapism of other etiology, is also disclosed.

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PROSTAGLANDIN E2 TREATMENT OF IMPOTENCE

Background of the Invention

The present invention relates to the treatment of impotence, and, more particularly, to the reversible pharmaceutical treatment of impotence using prostaglandin PGE_2.

In excess of about 10 million men in the United States alone exhibit sufficient erectile dysfunction that they can be characterized as effectively impotent. Impotence in the human male can arise from a variety of psychological and physiological etiologies. For example, long term diabetes, damage to the spinal cord, multiple sclerosis, or nerve damage resulting for example from lower abdomen or prostate surgery, and advancing age can result in impotence. For differing reasons, each of the foregoing result in an inability to pressurize the corpora cavernosa, which can result in turn from either an insufficient arterial inflow on the supply side, or an insufficient increase in the venous output resistance to blood flow.

A wide variety of mechanical means have been provided, in an effort to overcome erectile dysfunction. For example, United States Patent No. 4,596,242 to Fischell discloses a surgically implantable hydraulic system, having a fluid reservoir and pressure generator, a patient manipulable valve, a pressure reservoir and a distensible member responsive to actuation of the valve. A variety of other prior art mechanical implants and other devices for this purpose are described in the Background of the Invention section of United States Patent No. 4,596,242.

In addition to the mechanical efforts to overcome erectile dysfunction, pharmaceutical approaches have been tried as well. For example, prostaglandin E1 has been observed to produce erection in some cases, but only by direct percutaneous injection into the penis.

Notwithstanding the foregoing, there remains a need for an improved treatment of erectile dysfunction. Surgical

implantation and/or repeated injections range from disfavored to medically disadvantageous, and do not, as a whole, provide a satisfactory solution to the problem. From a patient usability standpoint, erectile dysfunction would most advantageously be treated on a self-administration basis, without the need for surgical intervention or repeated injections of a pharmaceutical agent.

Summary of the Invention

In accordance with one aspect of the present invention, there is provided a method of treating erectile dysfunction in a male patient, comprising the step of administering to the patient a unit dose of a formulation comprising an erectile dysfunction treating amount of a prostaglandin E2 compound, or pharmaceutically acceptable salts or derivatives thereof. The prostaglandin E2 compound is preferably formulated together with a pharmaceutically acceptable delivery medium, which may comprise local anesthetic agents and/or a lubricant. Preferably, the anesthetic agent comprises lidocaine.

A unit dose of the formulation in accordance with the present invention will typically be less than about 5 cc in volume, preferably less than about 3 cc and most preferably within the range of from about 1 cc to 2 cc. The amount of active ingredient in a unit dose will typically be within the range of from about 0.2 mg to about 5.0 mg. More preferably, the amount of prostaglandin E2 in a unit dose will be within the range of from about 0.6 mg to about 1.8 mg in a formulation not also including lidocaine, and from about 1.2 mg to about 3.6 mg in a formulation including lidocaine.

The administration step of the method in accordance with the present invention comprises the transurethral administration of the unit dose of formulation. In an embodiment where the formulation comprises a cream or gel form, the formulation is preferably transurethrally instilled or inserted such as by extrusion through a syringe or unit dose administration packet comprising an elongate tubular administration tip.

In an embodiment of the present invention, wherein the administrable form of the formulation comprises a relatively rigid suppository, the suppository can be manually inserted into the distal opening of the urethra.

In accordance with a further aspect of the present invention, there has been provided a formulation and method for relieving the erectile dysfunction treating effects of the application of a formulation comprising prostaglandin E2, or of treating priapism of other etiology. In accordance with this antidote method, an effective antidotal amount of a formulation comprising a 15 methyl substituted prostaglandin F2α or pharmaceutically acceptable salt is administered in the same manner as described above.

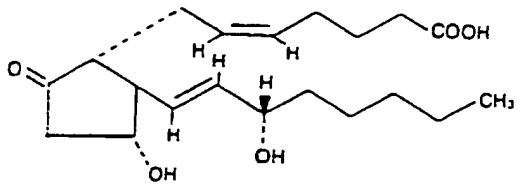
These and further objects and advantages of the present invention will become apparent from the Detailed Description of Preferred Embodiments which follows, considered together with the appended Claims.

Detailed Description of Preferred Embodiments

The prostaglandins are a series of cyclic derivatives of certain unsaturated fatty acids. They are found in a variety of tissues, including the prostate gland, the seminal vesicles, the lungs and the brain. These naturally occurring prostaglandins are derived by cyclization of 20-carbon unsaturated fatty acids such as arachidonic acid. See Lehninger, Albert L., Biochemistry, 2d ed. (1975), p. 300 (hereinafter "Lehninger").

Carbon atoms of the fatty acid backbone are cyclized to form a characteristic 5-membered ring. The prostaglandins are divided into a number of groups, including those designated A-F, based on the configuration of the ring structure. Prostaglandins also differ in stereochemistry and in the number of side chain double bonds which are conventionally indicated by a subscript number. Thus, for example, prostaglandin E_2 ("PGE_2") has the ring configuration characteristic of the E group and contains two side chain double bonds. The chemical name for PGE_2 is (5Z,11α,13E,15S)-11,15-Dihydroxy-9-oxo-prosta-5,13-dien-1-oic acid and the

structural formula of one form is represented in Formula I, below. The molecular formula is $C_{20}H_{32}O_5$.

I. 

The biosynthesis of prostaglandins has been well characterized. See, e.g., Lehninger at p. 687. In a typical biosynthetic pathway, exemplified by production of PGE_2, the essential fatty acid linoleic acid is converted into the 20-carbon arachidonic acid, which is then acted upon by prostaglandin synthase, a dioxygenase enzyme. Oxygen atoms are added at carbon atoms 9 and 15, and the product is cyclized by formation of a bond between carbon atoms 8 and 12. In the presence of reduced glutathione, this cyclized product undergoes conversion into prostaglandin PGE_2. Other types of naturally occurring prostaglandins are derived from different polyunsaturated fatty acids.

In about the 1960s, prostaglandins were isolated from a particular species of Caribbean coral, which made them more widely available for research. Catanzarite, Valerian A. and Gary Aisenbrey, Contemporary OB/GYN (October 1987), p. 22 (hereinafter "Catanzarite"). A large number of natural and synthetic analogues of the prostaglandins are now known. Lehninger at 687.

The prostaglandins are known to produce often unpredictable effects over a very wide range of biological activities of a hormonal or regulatory nature. Prostaglandins have been reported to both lower and raise blood pressure, to inhibit gastric secretion, dilate bronchi, inhibit lipolysis, antagonize vasopressin-induced anti-diarrhesis, constrict the

pupil, increase and decrease the intraocular pressure and produce contraction of the uterus. See, e.g., Ganong, William F., Review of Medical Physiology, 7th ed. (1975), p. 226 (hereinafter "Ganong"). The naturally occurring prostaglandins all appear to be capable of affecting the control of vascular and other smooth muscle contractions. In the central nervous system, prostaglandins are known to modify responses to certain synaptic transmitters. They have been reported to mimic the actions of some hormones and to inhibit the actions of certain others. See Ganong at 226.

Two of the most extensively studied of the prostaglandins are PGE_2 and $PGF_{2\alpha}$. Both of these molecules are synthesized within the pregnant and non-pregnant uterus. While PGE_2 and $PGF_{2\alpha}$ are similar in mediating some effects, they are different with respect to certain others. Both cause uterine contractions, but they predominate at different sites within the uterus -- PGE_2 in the lower uterine segment, $PGF_{2\alpha}$ in the fundal region. Both play important roles during labor, but PGE_2 has its major effect in cervical ripening, whereas $PGF_{2\alpha}$ is more important in generating uterine contractions. PGE_2 elevates body temperature, whereas $PGF_{2\alpha}$ has no apparent effect on body temperature. PGE_2 is a vasodilator and bronchodilator, while $PGF_{2\alpha}$ is a bronchoconstrictor and vasoconstrictor. See Catanzarite at 21-22.

Prostaglandins have been used in gynecology for pregnancy termination. Preparing the cervix with a prostaglandin suppository has been found to reduce the incidence of cervical laceration and significant bleeding. Catanzarite at 22. Synthetic analogues of prostaglandin PGE_2, such as 16-16-dimethyl PGE_2 and 9-methylene PGE_2, have proven useful for the induction of first trimester abortions. Such procedures typically use vaginal suppositories containing 20 milligrams PGE_2 or 3 milligrams of 15-methyl $PGF_{2\alpha}$, or by repeated intramyometrial injections of 15-methyl $PGF_{2\alpha}$, or by infusing a $PGF_{2\alpha}$-urea mixture (20 milligrams of $PGF_{2\alpha}$ and 40 milligrams of urea in 100 mL of 5% dextrose in water) into the amniotic sac.

In obstetrics, prostaglandins have been used for cervical ripening, labor induction and control of post-partum hemorrhage. Catanzarite at 29. For cervical ripening, PGE_2 has been given intravenously, orally and vaginally, but the preferred route is intracervically. A PGE_2 gel is now commercially available in Scandinavia, and another PGE_2 gel is being investigated in the United States. The PGE_2 gel can also be used for labor induction (3-5 mg of PGE_2, prepared by blending a 20 mg suppository with 60 mL of lubricating jelly and using 9-15 mL of the mixture, is placed in the vagina). Catanzarite at 32. Prostaglandins have also been utilized to control post-partum hemorrhage.

Since circulating prostaglandins can be rapidly metabolized in the lungs, liver and kidneys, a number of synthetically modified prostaglandins have been developed that are not metabolized as quickly. See, e.g., Catanzarite at 32.

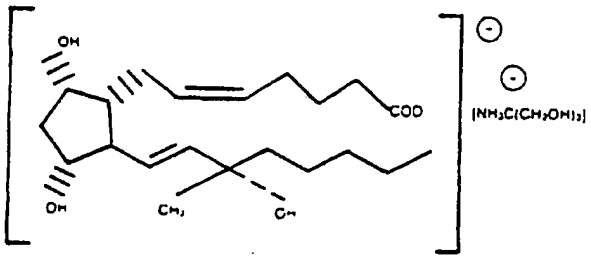
Prostaglandin PGE_2, also known as the "Prostin E2" brand of "dynoprostone," is available from the Upjohn Company in the form of a vaginal suppository. Indications and usage reported by Upjohn are (i) termination of pregnancy from the 12th through the 20th gestational week, (ii) evacuation of the uterine contents in the management of missed abortion or intrauterine fetal death up to 28 weeks of gestational age, and (iii) in the management of non-metastatic gestational trophoblastic disease (benign hydatidiform mole). See The Upjohn Co., Prostin E2 product description 810 994 009, Oct., 1990.

Contraindications to the use of prostaglandin PGE_2 include hypersensitivity to dynoprostone, acute pelvic inflammatory disease, or patients with active cardiac pulmonary renal or hepatic disease. Upjohn notes that although carcinogenic bioassay studies have not been conducted in animals for PGE_2 (because of the limited indications for use and the short duration of administration), there was no evidence of mutagenicity in either the Micronucleus Test or in the Ames Assay. Upjohn also indicates that a number of adverse reactions may be observed with the use of PGE_2 for

abortions. These adverse reactions are related to PGE_2's contractile effect on smooth muscle and include vomiting, temperature elevations, diarrhea, nausea, transient diastolic blood pressure decreases, and a number of other effects. Upjohn's vaginal suppository contains 20 mg of PGE_2 in a mixture of glycerides of fatty acids.

Upjohn markets an (15S)-15-methyl analogue of prostaglandin $PGF_{2\alpha}$ under the brand name Hemabate®, and also known as "carboprost tromethamine sterile solution." The structural formula of Hemabate® is represented in Formula II below:

II.



Upjohn reports that Hemabate® is indicated for aborting pregnancy between the 13th and 20th weeks of gestation, in certain conditions related to second trimester abortions, and in the treatment of post-partum hemorrhage. See The Upjohn Co., product description 814 350 002, Nov., 1989. For abortion, the prostaglandin solution is injected using a syringe and administered deep in the muscle. Intramuscular injection is also used for treating post-partum uterine bleeding.

Upjohn also markets prostaglandin PGE_1, as the "Prostin VR Pediatric" brand of "alprostadil sterile solution," which is used to temporarily maintain the patency of the ductus arteriosus until corrective surgery can be performed in neonates having congenital heart defects and who depend upon the patent ductus for their survival. For the administration of PGE_1 in neonates, Upjohn recommends continuous intravenous infusion into a large vein, or administration through an

umbilical artery catheter placed at the ductal opening. See The Upjohn Co., product description 811 987 004, in Physician's Desk Reference, 45th Edition, p.2250 (1991).

Quite surprisingly, the inventor herein has discovered that transurethral application of PGE_2 can in many cases provide an effective, reversible treatment of erectile dysfunction in human males. Thus, in accordance with one embodiment of the present invention, PGE_2 or a pharmaceutically acceptable salt, ester or other derivative thereof is formulated together with a carrier medium which may comprise any of a variety of additional excipients or adjuvants into a form suitable for transurethral delivery. In accordance with another aspect of the present invention, there is provided an antidote for reversing the effects of the foregoing PGE_2 treatment, comprising administration of an antidotal amount of a $PGF_{2\alpha}$, or pharmaceutically acceptable salts, esters or derivatives thereof. Preferably, 15-methyl $PGF_{2\alpha}$ is utilized for this purpose.

Preferably, the PGE_2 or $PGF_{2\alpha}$ formulation will comprise a cream or gel, although a more solid form such as pellets or a rod-shaped suppository body may also be used. Although low viscosity gels or liquids may also be formulated, the liquid form may present handling and delivery difficulties and may not present a sufficient dwell time in the urethra to permit absorption of an efficacious amount of the active ingredient.

Administration of the cream or gel form may be accomplished by transurethral delivery using a syringe without a needle, or with a short blunt cannula attached. The gel or cream forms are preferably provided in unit dose amounts for self administration by the patient. For this purpose, compressible unit does packages are preferably provided with an elongate tubular delivery spout, sized for transurethral insertion. Following transurethral installation of any of the liquid, gel or cream forms, the distal end of the urethra is preferably occluded, such as by manual pressure for up to several minutes, to permit sufficient dwell time for absorption.

Typically, a lubricant and/or a local anesthetic for desensitization will also be provided for use as needed. In one embodiment, the PGE_2, lubricant and anesthetic are all formulated into a convenient cream. This cream may be prepared, for example, by mixing one Upjohn Prostin E2® PGE_2 suppository together with 10cc of a lidocaine jelly such as Xylocaine® 2% jelly (available from Astra Pharmaceutical Products) and 50 cc. of a surgical lubricant such as K-Y jelly (available from Johnson & Johnson). Lidocaine HCl, available in a variety of formulations, comprises acetamide, 2-(diethylamino)-N-(2,6-dimethylphenyl)-monohydrochloride.

The amount of lubricant and the amount and concentration of anesthetic can be varied considerably as will be apparent to one of skill in the art. For example, lidocaine jelly can be used having anywhere from about 1% to about 10% and preferably about 2% lidocaine. Percentages much lower than about 1% are less desirable due to the requirement of a relatively large volume of jelly to deliver an effective dose of lidocaine. In general, the anesthetic level can largely be dictated by patient preference, as determined through routine experimentation. Although the incidence of adverse effects with Xylocaine® 2% jelly is very low, caution should be exercised when applying large amounts since the frequency of adverse effects is directly proportional to the total dosage of the local anaesthetic administered. See Astra Pharmaceuticals, product description 021838R11, June 1986; in Physician's Desk Reference, 45th Edition (1991), at p. 628.

A variety of other anesthetic agents can also be used with the formulation of the present invention, as will be appreciated by one of skill in the art. For example, novocaine, procaine, tetracaine or benzocaine may be selected. Patients allergic to para-aminobenzoic acid derivatives such as procaine, tetracaine and benzocaine have not appeared to show cross sensitivity to lidocaine. Lidocaine is also contraindicated in patients with a history of sensitivity to amide type local anesthetics. Xylocaine 2% jelly also contains methylparaben, propylparaben and

hydroxypropylmethylcellulose, as well as lidocaine; and, therefore, Xylocaine is contraindicated for patients with known sensitivities to any of these compounds. See Astra Pharmaceuticals, product description 021838R11, June 1986; in Physician's Desk Reference, 45th Edition (1991), at p. 628.

It has been determined by the inventor that the effect of the PGE_2 treatment is generally less pronounced when delivered in a formulation which also comprises lidocaine. Thus, in a lidocaine-containing formulation, the dosage of PGE_2 is preferably increased over that in a non-lidocaine-containing formulation, and more preferably, the PGE_2 dosage is preferably doubled in a lidocaine-containing formulation.

More or less lubricant may be desired depending upon the delivery dose and concentration of the anesthetic jelly. In general, the total volume of the impotence treating unit dose should be no more than about 5 cc, and preferably from about 1 cc to no more than about 2 cc due to the inherent capacity of the urethra. Doses of excessive volume can result in painful administration, and also in retrograde migration of the excess formulation into the prostatic urethra or bladder.

Preferably, the total amount of PGE_2 contained in a unit dose will be within the range of from about 0.2 mg to about 5.0 mg. Due to differing etiology of erectile dysfunction, and inherent variations across a population in terms of responsiveness to pharmaceutical agents, some routine experimentation may be desired to determine optimum dosages for a given patient or class of patients.

In general, however, doses within the range of from about 0.5 to about 5.0, and preferably from about 0.6 to about 3.6 mg PGE_2, have generally proven sufficient in patients in which a response is likely to occur. Although it is not possible to predict with precision what types of patient populations will likely respond to the treatments disclosed herein, certain classes of patients are anticipated to be treatable depending upon the etiology of the condition. For example, patients in whom erectile dysfunction is associated with vascular abnormalities such as atherosclerosis which prevents adequate

blood inflow are not likely to respond. Patients in whom the dysfunction is a result of such conditions as diabetes, denervation, or psychological status are expected to be more likely to respond.

In the antidotal or priapism treating PGF formulation, the PGF will generally be present in an amount within the range of from about 5 to about 50 μg per 1 cc dose of formulation, preferably within the range of from about 8 to 20 μg/cc and more preferably about 12 μg/cc. As with the PGE formulation, optimum dosage for a given patient can be determined through routine experimentation.

Any of several different delivery systems may be utilized in accordance with the method of the present invention. For example, if a fluid or cream or gel system is used, the carrier can be absorbed directly, or allowed to be expelled following sufficient dwell time which may be controlled by occluding the distal end of the urethra.

Alternatively, more solid delivery vehicles may be used such as an ovoid or rod-shaped suppository. Suppositories can be formulated from any of a variety of materials which exhibit sufficient physical integrity to permit trans-urethral insertion and which will then permit delivery of the medication. Once installed, the structural component of the suppository may break down under the influence of body heat. Alternatively, materials can be used which will dissolve in an aqueous environment at a pH within the range of that typical of the urethra. One suitable composition is a mixture of glycerides of fatty acids such as that used with the Prostin E2® product.

As a further alternative, a variety of drug delivery vehicles may be used which neither dissolve nor break down in the environment of the urethra. Relatively rigid rod-shaped delivery vehicles may be fashioned from materials having a microporous structure for the time release of entrapped pharmaceutical.

Such vehicles can be transurethrally inserted for a predetermined period of time and then removed following

delivery of an efficacious amount of drug. Although the convenience of a self dissipating carrier is lost, the removable time release delivery structure may have the added advantage of providing some range of flexibility in the total delivered dose. Thus, the patient, by leaving the implant in place for relatively shorter or longer periods of time, can optimize the dose within a preset maximum range.

Particular embodiments of the present invention will be described in the Examples which follow.

EXAMPLE I - Preparation of Intraurethral PGE_2 Cream

A batch of PGE_2 cream was prepared by mixing a 40 mg PGE_2 suppository (obtained as the "Prostin E2" suppository from the Upjohn Company) with 10 cc of 2% xylocaine jelly and 50 cc of K-Y surgical lubrication jelly (hydroxyethyl-cellulose, obtained from Johnson & Johnson). Mixing was accomplished by stirring until the mixture appeared homogenous upon visual inspection. The result was a PGE_2 cream having approximately 1.3 mg of PGE_2 per 2 cc of cream.

EXAMPLE II - Preparation of Intraurethral PGE_2 Gel

The homogenicity of a batch of PGE_2 is ensured by inclusion of a methylene blue marker. One 20 mg PGE_2 suppository ("Prostin E2" from the Upjohn Company) is sliced into thin slices and allowed to soften at room temperature for 15 minutes. A small drop of 1% methylene blue solution (American quinine, Shirley, New York) is placed onto each slice to serve as a marker for homogenicity. The softened slices are thereafter geometrically mixed with the contents of a 56.7 gram tube of K-Y jelly to yield a homogenous mixture, as evidenced by blue color uniformity. The theoretical content of the final product is approximately 0.67 milligrams of PGE_2 per 2 cc of gel.

EXAMPLE III - Preparation of Lipid Based Intraurethral PGE_2 Cream

A batch of PGE_2 cream in cocoa butter is prepared by placing one 20 mg. PGE_2 suppository (Prostin E2 by the Upjohn

Company) into a porcelain evaporating dish and is melted in a 37°C water bath. Shredded cocoa butter is added to the melted suppository with stirring to bring the total mass to approximately 20 grams. As the melting continues, the temperature of the mixture is kept at or below about 33°C. Higher temperatures are to be avoided, as they have been reported to cause the crystalline form of the cocoa butter to change, resulting in aberrations in bioavailability. Transformations in the crystalline form of the cocoa butter are visually observed as a change from opalescent to transparent. After complete melting, the mixture is stirred thoroughly and poured into suppository molds. The material is thereafter allowed to cool at room temperature for about 15 minutes, and thereafter is placed in the refrigerator to facilitate further solidification. The suppositories may thereafter be removed from the mold, individually packaged and placed in refrigerated storage under anhydrous conditions.

EXAMPLE IV - Administration of Intraurethral PGE_2 Cream

Two cc of the PGE_2 cream from Example 1 was instilled into the urethral meatus of each of 10 impotent male patients between the ages of 50 and 70, using a syringe. The cream was massaged down the urethra, and then the distal end of the urethra was occluded for 5 minutes by manual pressure.

EXAMPLE V - Efficacy of PGE_2 Cream in Treating Human Erectile Dysfunction

The effect of administration of PGE_2 cream, prepared and administered in accordance with the procedures of Examples I and IV, was observed. After 15 to 30 minutes, treatment response was rated as no penile tumescence, partial tumescence or full tumescence.

As a result, two of the ten men treated had no response, six had partial tumescence, and two had full tumescence. Thus, 80% of the men treated showed at least partial p nile tumescence in response to the intraurethral PGE_2 cream.

EXAMPLE VI - Efficacy of Lower Concentrations of PGE_2 Cream in Treating Human Erectile Dysfunction

PGE_2 cream was prepared and administered in accordance with the procedures of Examples I and IV, except that a 20 mg PGE_2 suppository was used instead of a 40 mg suppository. This cream contained approximately 0.7 mg of PGE_2 per 2 cc of cream. Two cc of cream was used to treat each of ten impotent men between the ages of 50 and 70. After 15 to 30 minutes, treatment response was rated as no penile tumescence, partial tumescence, or full tumescence.

As a result, four of the ten men treated had no response, two had partial tumescence, and four had full tumescence. Thus, even using lower concentrations of PGE_2, 60% of the men treated showed at least partial penile tumescence in response to the intraurethral PGE_2 cream.

EXAMPLE VII - Use of $PGF_{2\alpha}$ to Counteract Effects of Administration of PGE_2

Priapism resulting from the PGE_2 treatment in accordance with the present invention has been determined to be reversible or treatable through the application of an effective antidotal amount of a 15 methyl substituted prostaglandin F2α containing formulation. In addition, it is anticipated that priapism of a variety of other etiology will be similarly treatable.

An antidotal formulation is prepared by mixing approximately 250 micrograms of prostaglandin F2α obtained as Hemabate, marketed by Upjohn, in approximately 20 cc of K-Y jelly. Mixing is accomplished manually until visual observation reveals a homogenous composition. A dose of approximately 1 cc of the foregoing formulation is instilled in accordance with Example IV, to reverse the results of the PGE_2 treatment in accordance with the present invention.

Although this invention has been described in terms of certain preferred embodiments, other embodiments that are apparent to those of ordinary skill in the art are also within the scope of the invention. In particular, analogs or

derivatives of PGE_2 and $PGF_{2\alpha}$ which do not affect the basic functionality of those molecules as described herein are also considered within the scope of the present invention. Accordingly, the scope of the invention is intended to be defined only by reference to the appended claims.

I CLAIM:

1. A pharmaceutical formulation for treating erectile dysfunction, comprising an erectile dysfunction treating amount of prostaglandin E2 or pharmaceutically acceptable salt thereof and a delivery medium for the transurethral delivery of said formulation.

2. A formulation as in Claim 1, further comprising an anesthetic agent.

3. A formulation as in Claim 2, wherein said anesthetic agent comprises lidocaine.

4. A formulation as in Claim 1, further comprising a lubricant.

5. A formulation as in Claim 1, wherein said formulation is in the form of a cream or a gel.

6. An elongate drug delivery vehicle dimensioned for transurethral insertion, said delivery vehicle comprising the formulation of Claim 1.

7. A delivery vehicle as in Claim 6, wherein the structural integrity of said vehicle is provided by a material which softens under the influence of body heat.

8. A delivery vehicle as in Claim 7, wherein said delivery vehicle is a suppository.

9. A delivery vehicle as in Claim 6, wherein the structural integrity of said vehicle is provided by a material which is dissolvable in an aqueous environment.

10. A delivery vehicle as in Claim 9, wherein said delivery vehicle is a suppository.

11. A delivery vehicle as in Claim 6, wherein said delivery vehicle comprises a time-release drug delivery medium.

12. A pharmaceutical composition for use in treating erectile dysfunction, wherein said composition comprises an erectile dysfunction treating amount of prostaglandin E_2 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable delivery medium.

13. A pharmaceutical composition as in Claim 12, wherein said composition is delivered transurethrally.

14. A composition as in Claim 12, wherein said composition further comprises an anesthetic agent.

15. A composition as in Claim 14, wherein said anesthetic agent comprises lidocaine.

16. A composition as in Claim 12, wherein said composition further comprises a lubricating agent.

17. A composition as in Claim 12, wherein said composition is in the form of a cream or gel.

18. A composition as in Claim 12, wherein said composition is in the form of a suppository.

19. A composition as in Claim 12, wherein said erectile dysfunction treating amount of prostaglandin E_2 comprises within the range of from about 10 mg to about 50 mg of prostaglandin E_2.

20. A method as in Claim 13, wherein said erectile dysfunction treating amount of prostaglandin E_2 comprises within the range of from about 0.2 mg to about 3.6 mg of said compound.

21. Use of a pharmaceutical composition for the manufacture of a medicament for treating erectile dysfunction, wherein said composition comprises an erectile dysfunction treating amount of prostaglandin E_2 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable delivery medium.

22. Use of the pharmaceutical composition of Claim 21, wherein said delivery medium is administered transurethrally.

23. Use of the pharmaceutical composition of Claim 21, wherein said composition further comprises an anesthetic agent.

24. Use of the pharmaceutical composition of Claim 23, wherein said anesthetic agent comprises lidocaine.

25. Use of the pharmaceutical composition of Claim 21, wherein said composition further comprises a lubricating agent.

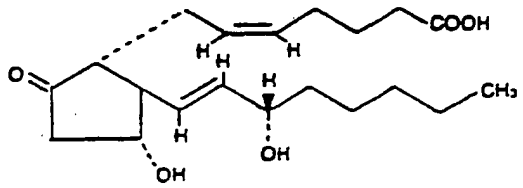
26. Use of the pharmaceutical composition of Claim 21, wherein said composition is in the form of a cream or gel.

27. Use of the pharmaceutical composition of Claim 21, wherein said composition is in the form of a suppository.

28. Use of the pharmaceutical composition of Claim 21, wherein said erectile dysfunction treating amount of prostaglandin E_2 comprises within the range of from about 10 mg to about 50 mg of prostaglandin E_2.

29. Use of the pharmaceutical composition of Claim 22, wherein said erectile dysfunction treating amount of prostaglandin E_2 comprises within the range of from about 0.2 mg to about 3.6 mg of said compound.

30. A method of treating erectile dysfunction in a male patient, comprising the step of administering to the patient a unit dose of a formulation comprising an erectile dysfunction treating amount of a compound having the structural formula:



or pharmaceutically acceptable salt or ester thereof, together with a pharmaceutically acceptable delivery medium.

31. A method as in Claim 30, wherein said administration step comprises the transurethral placement of said formulation.

32. A method as in Claim 30, wherein said administration step further comprises occluding the urethra distally of the formulation to prevent the escape thereof.

33. A method as in Claim 30, wherein said formulation further comprises an anesthetic agent.

34. A method as in Claim 33, wherein said anesthetic agent comprises lidocaine.

35. A method as in Claim 30, wherein said formulation further comprises a lubricating agent.

36. A method as in Claim 30, wherein said formulation is in the form of a cream or gel.

37. A method as in Claim 30, wherein said formulation is in the form of a suppository.

38. A method as in Claim 30, wherein said unit dose comprises within the range of from about 10 mg to about 50 mg of said compound.

39. A method as in Claim 31, wherein said unit dose of formulation comprises within the range of from about 0.2 mg to about 3.6 mg of said compound.

INTERNATIONAL SEARCH REPORT

Int. ational application No.
PCT/US92/05610

A. CLASSIFICATIO OF SUBJECT MATTER
IPC(5) :A61K 31/195 31/19
US CL :514/566, 573
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/566, 573

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	US, A, 4,311,707 (Birnbaum et al) 19 January 1982, see entire document.	1-5,12-20 1-39
Y	US, A, 4,801,587 (Voss et al) 31 January 1989, see entire document.	1-39
Y	DICP-The Animals of Pharmacotherapy, vol. 25 issued April 1991, Michelle J. Artoux. "Alprostadil In Impotence", pages 363-365 see entire document.	1-39

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be part of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 04 SEPTEMBER 1992	Date of mailing of the international search report 10 NOV 1992
Name and mailing address of the ISA/ Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. NOT APPLICABLE	Authorized officer LEONARD SCHENKMAN Telephone No. (703) 308-4651

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